BASELINE STUDIES IN CEREBRAL BLOOD FLOW: REPRODUCIBILITY AND DENSITY EFFECTS ASSOCIATED WITH A SIMPLE VISUOSPATIAL TASK

By

JANET COPELAND FALGOUT

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To my family and my friends,
who have cared for me throughout
this most solitary of pursuits.

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It is generally true that the motivation to identify oneself as a member of any profession derives in no small part from contact with—and certainly from respect and admiration for—those individuals who represent that profession with distinction and integrity. I am fortunate to be able to claim several of these individuals as members of my supervisory committee: Dr. Eileen Fennell (chair), Dr. Hugh Davis, Dr. Jacquelin Goldman, Dr. Russell Bauer, and Dr. Edward Valenstein. These people—each in his or her unique capacity—have been my teachers in many different ways for many years. Without their influence and support, I would not have been able to reach this point in my education. Without their personal attributes, I would not have wanted to. I am glad to have the opportunity, in these formal acknowledgments, to publicly recognize their influence in my personal and professional development, and to express my very sincere and deeply felt gratitude.

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BASELINE STUDIES IN CEREBRAL BLOOD FLOW:
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By

Janet Copeland Falgout

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Repeated measurements of cerebral blood flow (rCBF) were made using the 133-xenon inhalation technique in two within-group studies: (1) under normal resting (NR) and visuomotor task conditions, and (2) during performance of the visuomotor task at two different rates. Twelve healthy right-handed males ages 19-35 served as subjects in each study. Analysis of variance revealed substantial reduction in run-to-run variability of rCBF during the visuomotor task as compared to the non-task condition. While no major differences in level of flow were indicated by comparisons between visuomotor and NR measures, significant individual differences were associated with rate of task presentation. The hypothesized stabilizing function of a "controlled-rest" condition in sequential studies—and of its alias, the "sensorimotor control task" in studies of complex cognitive processes—is validated by these studies.

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INTRODUCTION

In the study of brain-behavior relationships there are very few ways in which the physiologic correlates of cognitive or sensorimotor behaviors can be directly assessed in healthy, alert individuals. Most common among these methods are the electrophysiologic techniques (EEG and its computer-assisted derivatives, e.g., averaged evoked potential and power spectrum analysis) and the radioisotopic techniques, including the older two-dimensional cerebral blood flow methodologies and the newer three-dimensional tomographic methods of estimating cerebral metabolic activity. These techniques, each with its respective limitations and strengths, offer us the opportunity to observe certain parameters of the intact human brain in various functional states.

While certainly less sophisticated than the three-dimensional physiologic imaging techniques now becoming clinically accessible, the two-dimensional autoradiographic methods have proven both adequate and useful in the elucidation of brain function dependent on cortical gray-matter activity. Among these two-dimensional techniques, the ^{133}Xe inhalation method of measuring cerebral blood flow has been widely used in the study of normal brain function. Its nontraumatic attributes and utility in assessment of both cerebral hemispheres simultaneously have made it much preferable to the injection methods for use with healthy human subjects. Its relative cost efficiency and the capacity for repeated metabolic measurements over a relatively brief span of time give it more versatility than most other radioisotopic methods. It

remains an important tool in establishing refined experimental procedures which can be constructively adapted to studies utilizing more modern and costly tomographic techniques.

With the ^{133}Xe inhalation technique, the cerebral circulation is measured by introducing a trace amount of diffusible radioactive isotope into the bloodstream and recording its rate of clearance through the skull by external radiation detectors. The gaseous isotope is introduced through a rebreathing system which allows for monitoring the expired-air concentration of radioactivity, in order to correct for recirculation factors in the head clearance curve. Computation of cortical or gray matter flow parameters is based on mathematical models developed by Mallett and Veall (1965; Veall & Mallett, 1966), improved by Obrist and Risberg (Obrist et al., 1967; 1975; Risberg et al., 1975) and reformulated by Hazelrig et al. (1981) to utilize the total head clearance curve.

The inhalation method has been shown to correspond closely to the intracarotid injection method of measuring cerebral blood flow (Reivich et al., 1975). The injection method has been shown to reflect metabolic changes related to functional neuronal activity levels (Raichle et al., 1976). Both methods have been shown to be sensitive to changes in cerebral blood flow associated with sensorimotor or complex cognitive tasks (Halsey et al., 1979, 1980; Ingvar & Risberg, 1965, 1967; Larsen et al., 1977; Maximilian, 1980; Risberg & Ingvar, 1972, 1973; Wood et al., 1980). The total curve method of analysis (Hazelrig et al., 1981) has been found to be particularly sensitive to blood flow changes associated with simple sensorimotor tasks (Leli et al., 1985).

The standard procedure for obtaining a measurement of regional cerebral blood flow (rCBF) for an individual has required that the subject lie quietly at rest with eyes closed while the face mask and detectors are adjusted, ^{133}Xe is

administered, and isotope uptake and clearance is monitored for 10 minutes following a one-minute inhalation period. This so-called "normal rest" measure is often repeated as a validity check, or the subject may be required to perform an "activation" task during a subsequent inhalation and clearance period in order to obtain a measure of task-related cerebral blood flow. Such task-related measures have the potential for significantly increasing our fund of information in both clinical/diagnostic and neuropsychologic applications. In clinical application, for instance, it is reasonable to expect that the measurement of a person's ability to efficiently mobilize his metabolic resources (blood flow) on demand would yield more predictive information than simple determination of flow rate during an ill-defined or uncontrolled state of rest. In neuropsychologic research, the utility of physiologic data relating to localization or specialization of function is of obvious value in refining our understanding of brain-behavior relationships and individual variability. However, the optimal use of rCBF measurements—whether resting or activated, and whether for clinical or research application—requires that we obtain reproducible measurements of flow in relation to well defined behavioral states.

The importance of reproducible measurements becomes apparent when one notes that the run-to-run variability of the regional resting flow for the ^{133}Xe inhalation method averages about 7 percent across all detector locations in normal subjects (Blauenstein et al., 1977; Meyer et al., 1978). Individual regional values, however, ranging up to 50 or 100 percent from one measurement to the next are not uncommon, particularly in sleep-deprived subjects (Falgout et al., 1983). When such extreme variability is observed between two measures taken during a single session for an individual subject, the practical informational value of the rCBF measured in this "normal resting state" must be questioned. The uncontrolled variability becomes even more

problematic when measures are made over extended periods in patients for clinical purposes, or when resting baseline values are used for evaluation of task-related cognitive activation effects. These task-related rCBF activation effects typically range from 5 to 20 percent greater than the resting baseline—with a range similar to that of the run-to-run variability of the resting measures.

In an effort to reduce some of the extremes of state-related run-to-run variability in the measures of resting flow, the concept of a "controlled rest" measure has been introduced (Stump et al., 1978; Falgout et al., 1983, 1984) and is currently being tested in our laboratory. Such a measurement requires that the subject engage in a low-demand task which requires a continual (though minimal) focus of attention and a minimal motoric response throughout the inhalation period. Additionally, the sensorimotor control task, a low-demand task utilizing the same input and output modalities as the primary complex activation task under study (Wood, 1980; Leli et al., 1984), has been incorporated into our experimental design as a standard against which to measure cognitively mediated rCBF activation associated with the complex task (Leli et al., 1982, 1983; Hannay et al., 1983; McLain et al., 1984). It is with the aim of refining our knowledge of these baseline tasks that the following studies are presented.

DEFINITION OF PROBLEM

The hypothetical utility of a minimal-effort, controlled rest task in rCBF studies can be intuitively appreciated: A person who is continuously engaged in a simple, nearly automatic task—but one which requires an overt, observable response—is less likely to drift into those ill-defined dreamlike states which border on sleep than one who is asked merely to remain alert but silent and motionless, with eyes closed, for the 15-20 minutes necessary to complete a measurement of cerebral blood flow. Therefore, the psychophysiologic conditions under which a measurement is made are much more easily defined, since we have some idea of what the subject is doing, in addition to what he is not doing. In providing a continuous performance task to engage even a minimal portion of his attentional and motivational capacity, we are setting both implicit and explicit limits on the behavior we expect to observe during the course of the measurements. The more explicitly the task is defined, the more confident we will be in predicting the behavioral response to the testing situation, both within and between persons; we would hope that the associated physiologic responses would also reflect that predictability. To date, however, the stabilizing effect of such minimal-demand tasks on baseline rCBF measures has been hypothesized, but not demonstrated.

In our own laboratory, studies have been designed to assess reproducibility issues within same-session and split-session paradigms for controlled-rest tasks, and to evaluate the stability of the controlled-rest flow when a complex

activation-task measurement is interposed between control measures (McLain et al., 1984). Preliminary analysis suggests that the use of a simple visuomotor controlled-rest task may limit the extremes of variability associated with the normal rest measurement: The run-to-run variance of rCBF for the controlled-rest task is generally lower than that found in analogous normal-rest paradigms. However, the variability inherent in small-group samples limits the generalizability of these between-group findings. That is, an apparent decrease in variability attributed to the use of a controlled rest task may be due more to sampling artifact than to task effects. The more rigorous test of these preliminary findings requires that we administer both types of baseline conditions ("normal" rest and "controlled" rest) to the same sample of individuals. We will then be in a better position to evaluate the effects of a controlled rest task on regional cerebral blood flow measurements, in regard to both mean level of flow and reliability of the measures.

There is in addition a need to begin to define the effects of rate of task presentation on cerebral blood flow parameters. Our understanding of rCBF changes associated with complex cognitive activity is otherwise limited. An interpretational problem encountered in one of our own rCBF studies may be useful in illustrating this point.

For several practical reasons, the sensorimotor control tasks used as a reference baseline for the cognitive activation tasks in our first studies (Leli et al., 1982; Hannay et al., 1983; McLain et al., 1984) have been presented at a constant rate for all subjects, while the activation task has been self-paced. The necessity of using a counterbalanced design to minimize potential order effects was the major design factor precluding an equal rate of presentation of the control and activation tasks: in half the cases, an individual's average rate of activation task performance would not be known until after the control task

had been administered. It was assumed that a rate of control task presentation which was estimated to equal or exceed the average activation task performance would provide the most conservative estimate of rCBF effects associated with the sensorimotor components of the activation task. It was assumed, in other words, (a) that rCBF would increase in direct proportion to the number of task items completed per unit time, and (b) that this relationship would hold true both for simple sensorimotor and for complex cognitive tasks. Task-related blood flow changes associated with the cognitive components specific to the complex task, then, could be sorted out by comparing rCBF activation during complex task performance to the levels obtained during sensorimotor task performance.

In fact, in an initial study of a right-left discrimination task (Leli et al., 1982), when correlations were computed based on relative rCBF change scores (rCBF for activation compared to control) versus measures of task accuracy or total number of problems solved, the relationship was found to be an inverse one: individuals who completed more problems showed a smaller rCBF increase than those who worked more slowly. By design, as explained above, all individuals had completed a preset number of control tasks, which equaled or exceeded the number of self-paced activation tasks completed. Reasoning that the sensorimotor components of the complex activation task, if nothing else, would require cumulatively more neuronal activity (and therefore increased rCBF) for those subjects who performed a greater number of the complex task items, it seemed clear that the inverse relationship between rCBF and task performance measures could not be attributed to the sensorimotor differences between the two tasks: the correlation in that case would have to be a positive one. Consequently, an "effort" hypothesis was generated, among other possibilities, to account for the inverse relationship. Note again, however, that

this interpretation was grounded on an untested assumption: that more input/output per given period of time results in higher measured rCBF levels, even for simple sensorimotor tasks.

We actually know very little about what we can expect and what we can count on in measurements of rCBF in human subjects either at rest or while performing an imposed sensorimotor or cognitive task. The current series of studies continue to examine various parameters of the baseline measurement in rCBF. In particular, the two studies presented here examine the hemispheric and regional cerebral blood flow effects of a simple visuomotor task at two different rates (VMf and VMs) with respect to the following null hypotheses:

(1) Task effects: VMf mean flow is not different from resting mean flow.

(2) Rate effects: VMf mean flow is not different from VMs mean flow.

(3) Reproducibility: (a) Mean run-to-run variability of the resting flow is not different from mean variability of VMf flow, and (b) Mean run-to-run variability of VMf flow is not different from mean variability of VMs flow.

The visuomotor task rates selected for study represent the extremes of those achieved by individual subjects in previous self-paced cognitive activation studies, the faster (VM_f) averaging 7 sec. between stimuli, the slower (VM_s) having an average interstimulus interval of 14 sec. By comparing the effects of the higher-rate task to normal rest measures in the same group of subjects, one would ideally document an increased run-to-run reliability of the visuomotor task without a significant change in mean level of flow. By comparing the two rates of task presentation within a second group of subjects, one would hope to document minimal differences in both level and variability of flow between the two task rates. The findings of increased rCBF stability, combined with

minimal change in mean level of flow, would verify the utility of controlled rest or sensorimotor tasks in both clinical and experimental studies of human brain function.

LITERATURE REVIEW

In reviewing published research which might aid in formulation of predictions regarding the studies, there are three areas of particular relevance: (1) task effects; (2) reproducibility; and (3) rate-of-presentation, or density effects.

In the evaluation of task effects the primary question is whether the rCBF measures associated with performance of a simple visuospatial task differ significantly from those associated with the eyes-closed, resting state. There is every reason to expect that they should. There are several ^{133}Xe cerebral blood flow studies which have used visual stimuli in activation tasks of varying complexity (Risberg et al., 1977; Gur & Reivich, 1980; Roland & Skinhoj, 1981; Leli et al., 1982). In general, the results have shown bilateral activation—relative to eyes-closed rest—of the visual associative and posterior parietal cortex for simple, diffuse stimulation, with increased frontal involvement as task complexity and the need for focused attention increase. There is in addition the suggestion from studies using positron emission tomography to estimate glucose metabolism that right hemisphere activation (again in comparison to the eyes-closed resting state) may be relatively greater than left for tasks requiring attention to extra-personal space (Gur et al., 1983). However, among the visual activation tasks reported in the research literature which have required an overt response, most have used the verbal, spoken modality. Since the expected mode of response is likely to be critical in the

organization of a whole set of psychophysiologic behaviors, we would expect response modality to affect the organization of neural activity as well. Indeed, Leli et al. (1984), in attempting to assess the effects of spoken vs. manual response modalities using the inhalation technique, have demonstrated major differences in regional blood flow activation dependent on response modality. The visuomotor task used for the Leli et al. (1984) study, in fact, serves as the closest approximation to the visuospatial task at issue here, and may serve as the best model for predictions of task effects for the present study.

In the Leli et al. (1984) study, a simple number-recognition task utilizing a manual (button-press) response and presented at a 7-second rate produced significant rCBF increases (vs. rest) averaging 8 to 11 percent at bilateral temporo-occipital and posterior parietal detector locations. While the task induced flow increases in both cerebral hemispheres, the right hemisphere increases were on the average higher than those for the left, even for these numerical stimuli requiring a right-handed response. We might expect, then, similar results from performance of a visual task requiring simple pattern recognition and using the same motoric response mode and a similar rate of task presentation.

In making any task-to-rest comparisons of rCBF measures, of course, we are glossing over the whole issue of intrinsic run-to-run variability in the resting measures which led to the search for more reliable baseline or reference measures in the first place. Thus, the evaluation of task effects relative to rest may be of interest only if, and to the extent that, the effects are strong and consistent across individuals. A more basic concern may be the question of run-to-run variability of the resting and task-related rCBF measures.

Although reproducibility—or reliability, as it is more often called—has been evaluated in many rCBF studies under resting, non-stimulated conditions

in normal subjects (Obrist et al., 1975; Blauenstein et al., 1977; Stump et al., 1978; Larsen et al., 1977; McHenry et al., 1978; Meyer et al., 1978), only a few have addressed this issue using activation or task-related measures. With subjects who underwent two rCBF measurements while working on parallel forms of a complex reasoning task (Raven's Progressive Matrices), Risberg et al. (1977) reported a mean relative decrease in cerebral blood flow in frontal regions on second testing, while activation in posterior regions persisted. Maximilian (1980) also reported an initial activation to simple auditory (verbal) stimulation which disappeared upon second testing.

Studies in progress in our own laboratory have begun to evaluate task-repetition effects both within the same rCBF session and between sessions separated by a week or more, using both simple and complex tasks. Preliminary results for the visuomotor task under discussion suggest that same-session level-of-flow effects are reproducible: that is, the regional and hemispheric means are not significantly different from each other when the task is repeated up to four times on the same day, whether or not a more difficult cognitive task is interposed. In order to more accurately assess the relative run-to-run reliability of the rCBF associated with the visuomotor task in comparison to resting measures of rCBF, however, we are obliged to obtain both sets of measures from the same individuals. If successful, the major effect of a simple task such as the visuomotor task under study would be to stabilize run-to-run variability of the rCBF measures as compared to the normal resting state (Stump et al., 1978; Falgout et al., 1983, 1984). This effect would be obtained regardless of the task effects defined by rate or level of flow relative to resting baseline.

The final topic of interest here, task rate effects on cerebral blood flow, is an issue which is very nearly independent of, though certainly complementary

to, the assessment of task vs. rest effects. The primary question involves the comparison of rCBF effects associated with the same task at two different rates: Would task presentation differing in rate by a factor of two have a significant, consistent or predictable effect on hemispheric or regional rCBF? The only systematic investigation of rate effects on rCBF was reported by Fox and Raichle (1984) using the $H_2{}^{15}O$ tracer method with positron emission tomography (PET). Patterned photic stimuli were presented at rates ranging from 0.0 to 61 Hz to obtain eight sequential rCBF measures from each subject. The subjects were not required to make stimulus-related responses. A monotonic rCBF increase at the primary visual cortex was noted, linear between 1.0 and 7.8 Hz, and declining thereafter. Since stimulus rates below 1.0 Hz were not evaluated, and since the combination of sensory, motor, and volitional factors requisite to a sensorimotor control task were not present, we are not able to gain much information from this study about the expected rate effects in one of our cognitive activation studies. We can hope, but cannot presume, that rate effects will be negligible at low rates of presentation.

The purpose of this research is twofold: (1) to examine the effect of a minimal-effort, sustained-attention, visual-motor task on the level of flow and within-session reproducibility of regional cerebral blood flow (rCBF) measurements, and (2) to examine the rCBF changes related to a high vs. low rate of repetition of that task, i.e., task rate effects. These studies focus directly on the question of what rCBF effects we can reliably obtain in a young, healthy, non-patient population. Moreover, they examine assumptions that are central to the interpretation of rCBF effects attributed to complex cognitive tasks. Their import lies both in the predictive utility of the ^{133}Xe inhalation technique as a clinical tool, and in the theoretical utility of the method in neurobehavioral research. We would hope that these findings would be of value

as well in establishing experimental paradigms for research using the newer three-dimensional radioisotopic techniques to study the working brain.

MATERIALS AND METHODS

Sample Characteristics

Twenty-four healthy, right-handed, nonsmoking men ages 18 to 35 were selected from volunteers within the local community. They were interviewed to rule out major medical or psychiatric disorders, head trauma or other neurologic disorders, history of learning disability, hypertension, asthma, or allergic or sinus disorders that might impair normal breathing. They were informed of risks and procedures in conformance with guidelines for human use issued by the Institutional Review Board for the University of Alabama at Birmingham. The 24 men were randomly assigned to one of two experimental studies: a Task Effects study and a Density or Rate Effects study. They were paid $20-$30 each for their participation, depending on the amount of time involved.

Apparatus

rCBF data collection system. The rCBF data collection system has been described in detail for our laboratory by Wilson et al. (1977). In brief, there are three major components:

(1) A rebreathing system for administering ^{133}Xe and monitoring the expired-air concentration of CO_2 ($PeCO_2$).

(2) A collimated NaI scintillation detector system with amplifiers for monitoring the rate of ^{133}Xe clearance through the skull and one

for monitoring the expired air concentration of ^{133}Xe. The head detectors are arranged in two sets of eight and mounted on guide tracks to assure replicable placement close against the lateral sides of the subject's head (see Fig. 1).

(3) A computer system for processing of ^{133}Xe data. For each rCBF measurement, the air curve is sampled at 0.2 sec intervals, while counts from the head detectors are sampled at 2.0 sec intervals for 11 minutes after inhalation begins.

Stimulus-response system. The stimulus-response system for the administration of visual tasks during rCBF measurement consists of a Kodak Carousel projector connected to an auxiliary timer, a projection screen located approximately 5.5 feet above the subject (who lies supine), and a set of four small red indicator lights located horizontally under the screen, which are activated by a thumb depression switch held in the subject's right hand.

Procedures

General. Four separate 11-minute measurements of rCBF were obtained during one 2-hour session for each individual. Before undergoing the rCBF measurements, each person had the procedures and purpose of the study explained in detail, signed an informed consent, and filled out standard questionnaires relating to personal history and habits.

rCBF measurement. The measurement of rCBF requires the subject to recline on a hospital bed with his head resting between two adjustable detector blocks. He breathes through an oxygen-type molded rubber mask fitted securely over his nose and mouth during the rCBF measurements. The computer operator and technician work beyond his range of view, and room lighting is subdued during the measures. There is constant low-frequency noise

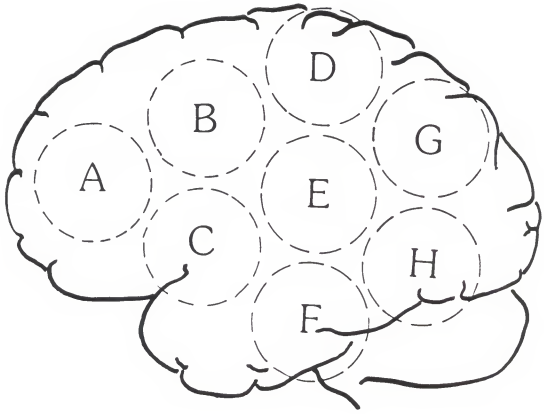

Figure 1. Schematic representation of approximate detector location over eight regions of the left hemisphere. The detector montage is duplicated over the right hemisphere.

from a large exhaust fan and the various equipment fans, so that the sound of the projector's advance is masked considerably.

Task descriptions. There are two basic types of tasks these subjects are asked to perform during the rCBF measurements: the 'normal-rest' (NR) task and the visuomotor (VM) task. The visuomotor task is presented at one of two rates as explained below, so that effectively there are three conditions under which rCBF measurements may be made: NR, VM-fast (VMf) or VM-slow (VMs). Each subject in fact undergoes four rCBF measurements under only two different conditions, depending on the study to which he is assigned.

Stimuli. The NR condition requires no external stimulus presentation. The VM task uses a series of slide-projected black-on-white line drawings as stimuli. Each slide presents an array of four horizontal and four vertical lines in which one of the vertical lines is crossed at the top, as in an upper-case "typed T" (see Fig. 2 for two examples). These slides are advanced at 5 to 9 second intervals (averaging 7 seconds) in the VM-fast condition, and at 10 to 18 second intervals (averaging 14 seconds) in the VM-slow condition. The stimuli are projected onto an overhead screen using the high intensity setting of the Kodak projector in a darkened room. The size of the illuminated field is 40 cm wide x 30 cm high, at a distance of 140 cm from the subject's eyes, and subtending a visual angle of approximately 16 degrees.

Instructions. For the NR condition the subject is instructed: "Just relax, with your eyes closed, and try not to move around during the blood flow measurement. We want you to remain alert but comfortable, and to breathe as normally as possible throughout the measurements." The resting condition is begun one minute before the rCBF measurement begins.

For the VM conditions, the subject is instructed: "For each slide you must indicate, by moving the light with this thumb-press button, which vertical line

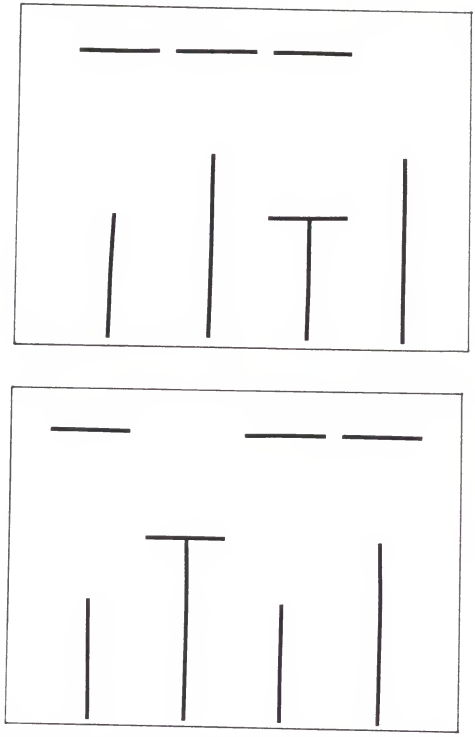

Figure 2. Examples of stimulus slides for the visuomotor tasks. In each slide, one of the four vertical lines is crossed at the top. Recognition of this 'target' must be indicated by illuminating the red indicator light beneath it, using a thumb-press trigger held in the right hand. The slides are presented with an average interstimulus interval of 7 seconds (range = 5 to 9) for the high-rate visuomotor task (VM_f), and at an average interstimulus interval of 14 seconds (range = 10 to 18) for the low rate task (VM_s).

is crossed by a horizontal one. The light will clear itself as the slide changes. There are no hidden problems or patterns you need to notice, the purpose is merely to give you a simple visual-motor task to work on during the blood flow measurement. Let your eyes scan the visual pattern and use the least motion necessary to press the button with your thumb. Breathe as normally and regularly as you can, and try not to move around during the measurement." The subject is allowed to practice on four slides, and begins the VM task one minute before the CBF measurement begins.

Order of tasks. Since the ^{133}Xe inhalation technique is a costly one (and healthy, non-smoking volunteers are at a premium), only those temporal permutations of the measurement conditions which are most relevant to interpretation of our other rCBF studies were used. Due to the limitation of four rCBF measurements per year for non-patient volunteer subjects, two studies were required for the evaluation of three measurement conditions and associated run-to-run variability. Each study used one group of 12 subjects.

The first study, designated the Task Effects study, allows for comparison of the differential effects of the normal resting vs. the visuomotor task on (a) level (or rate) of hemispheric and regional cerebral blood flow, and (b) variability of flow from one measurement to the next.

The second study, designated the Density Effects study,[1] allows for comparison of the effects of the visuomotor task at two different rates of presentation on (a) level of hemispheric and regional flow, and (b) variability of flow from one measurement to the next.

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[1]A note regarding terminology is in order here vis-a-vis the distinction between "rate" and "density" effects in rCBF studies. If two rates of stimulus presentation are to be compared, one double the other, a simple "rate" effect is one which would be obtained by monitoring rCBF for an equal number of stimulus/response cycles at each rate of presentation; that is, by halving the

Within each study, subjects were randomly assigned to one of four orders of task performance:

Order Model	Study 1 Task Effects Study	Study 2 Density Effects Study
A-B-B-A	VMf-NR-NR-VMf	VMf-VMs-VMs-VMf
B-A-A-B	NR-VMf-VMf-NR	VMs-VMf-VMf-VMs
A-B-A-B	NR-VMf-NR-VMf	VMf-VMs-VMf-VMs
B-A-B-A	VMf-NR-VMf-NR	VMs-VMf-VMf-VMs

Thus, each subject underwent four rCBF measurements (twice for each of two different task conditions) during one 2- to 2½-hour session. These permutations permit the evaluation of task effects, rate effects, and reproducibility effects related to both task and task rate, according to the hypotheses stated above.

Blood flow index. The blood flow index of interest here is f_1, representing primarily the fastest-clearing tissue in the brain, or gray matter flow (Obrist et al., 1975), and expressed in ml 100 g^{-1} $min.^{-1}$ It is derived according to the total head curve method of analysis (Hazelrig et al., 1981) for eight detector locations over each hemisphere (Fig. 1).

Physiologic data. Arterial CO_2 is estimated from end-expired air concentrations ($PeCO_2$). Blood pressure is recorded with a manual sphygmomanometer before each rCBF measurement. The estimated mean

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time period of task performance while presenting a constant or equal number of stimuli. Such studies are possible in physiologic studies (such as EEG) which have a sufficiently brief or variable period of data analysis. However, since the sampling window is set in rCBF studies to encompass a period of 10-12 minutes, doubling the rate of stimulus presentation also doubles the total number of stimulus/response cycles which are sampled in that window. Therefore, the term "density" is more accurate than "rate" in describing the effects which are addressed in this study. Having recognized this distinction, however, I will proceed to use the two terms interchangeably, and have even favored the use of "rate" in most instances, because I believe this is the concept most readily appreciated by most readers.

arterial blood pressure (MABP) is calculated from systolic (SBP) and diastolic (DBP) pressures according to the formula MABP = DBP + 1/3 (SBP + DBP).

Statistical Methods

Statistical analysis of the rCBF data is approached in two ways. First is the standard analysis of variance (ANOVA) approach used in previous studies to test for task-related effects on mean level of flow. Second is a variance components analysis to assess run-to-run variability of rCBF under different task conditions. The general procedures are outlined below.

(A) To assess for task and task rate effects on mean level of flow:

(1) The data from each study are examined for normality and homogeneity of variance.

(2) The data are screened by covariate analysis for each detector location to determine whether age, $PeCO_2$, or MABP account for a significant portion of the variance in a one factor, mixed model, repeated measures ANOVA which treats Subject as a random between-subjects variable and Treatment as a two-level within-subject factor (Myers, 1972, Ch. 7). The GLM Procedures developed by SAS Institute, Inc. (1982) are used for the analyses of variance and covariance.

(3) If covariates do not add significantly to the fit of the model, a reduced-model repeated-measures ANOVA is run for each detector location with f_1 as the dependent variable. Again, Subject serves as a random between-subjects factor that adjusts for those individual differences in initial or average level of flow which invariably account for the greater portion of variance in rCBF studies. The Treatment factor is a within-subject factor with two levels for each study.

(4) When uncertainty exists regarding assumptions of normality or homogeneity of variance, rank order ANOVAs are computed to verify significant findings (Winer, 1971, p. 301).

(B) To assess for within-subject run-to-run variability of one task vs. another, the VARCOMP procedure (SAS, 1982) is applied to the rCBF data (f_1) from each study after sorting by type of task. Thus, the total test-retest Subject variance for the two NR measurements in the Task Effects study can be partitioned into between-subject and within-subject (or error) components for that task, and the error component can be compared (by F-ratio computation) to the error variance component from the VM_f task for that study.

In anticipation of the results to be presented, it should be noted that the application of F-tests to comparison of the within-subject variance components computed for each type of task produces results similar to those of Cochran's C or Hartley's F_{max} statistics for testing homogeneity of variance (Winer, 1971, p. 205). In this sense, the discovery that within-subject error (i.e., test-retest) variance is significantly different depending on type of task (Study 1) should, strictly speaking, raise questions about application of analysis of variance techniques to those data. However, the F-ratios obtained in this study, while certainly significant within the context of a response-variability assessment, are not of sufficient magnitude to create a major methodologic concern among those who espouse the ANOVA techniques (Myers, 1972, pp. 72-76). The practical effects of a difference in error variance, in any case, should be to inflate α, the probability of a Type 1 error; that is, the probability of rejecting a true null hypothesis. This distortion is minimized when sample sizes are equal.

One suggested method of handling the problem (if it is one) of heterogeneity of variance prior to ANOVA is by corrective transformation of

the data to achieve homogeneity. While such preliminary transformation seems appropriate when sample sizes are larger and trends are apparent, consistent, or physiologically meaningful, an arbitrary, ad hoc transformation does not seem to be indicated when sample size is limited and trends are not evident. Likewise, in following up those analyses where ANOVA results indicated non-additivity in the model (Study 2), attempts at corrective data transformation were avoided. Regression/correlation analysis was applied, instead, in an attempt to define the nature of the interaction effects.

RESULTS

Study 1: Task Effects

The first study compares regional and hemispheric rCBF measures obtained during normal rest (NR) and visuomotor task (VM_f) conditions in a group of 12 right-handed males.

Table 1 contains the means and standard deviations of $\underline{f_1}$ values for the NR and VM_f tasks at each detector location (LOC) and for the left and right hemispheric means (LM and RM). The $\underline{f_1}$ value for each task represents a group average over two rCBF measures for each subject. Figures 3 and 4 graphically present the $\underline{f_1}$ means and standard errors of the means for the NR and VM_f tasks. The means of the physiologic measures, MABP and $PeCO_2$, did not differ significantly between NR and VM_f measurement conditions.

Analysis of covariance for each region revealed no significant or systematic effects of age, $PeCO_2$, or MABP which were not adequately accounted for by the Subject factor. Reduced-model repeated measures ANOVAs for each region to test for mean differences due to task effects revealed no significant F-ratios for Task at any region except RF, the right hemisphere inferior temporal detector ($p(>F) = .03$). At RF, the mean flow for the VM_f task is 5% higher than that for the NR condition. Most of the variance in the model at all regions is accounted for by the random Subject factor, and there are no significant Subject x Task interactions.

TABLE 1. F_1 (ml 100 g^{-1} min^{-1}) Means and Standard Deviations for Task Effects Group at Detector Locations Identified in Figure 1.

LEFT HEMISPHERE				RIGHT HEMISPHERE			
LOC[a]	TASK	MEAN[b]	S.D.	LOC[a]	TASK	MEAN[b]	S.D.
L	VM_f	77.2	12.8	R	VM_f	78.7	14.1
A	NR	78.7	15.4	A	NR	80.0	16.0
L	VM_f	77.5	12.3	R	VM_f	78.6	13.0
B	NR	77.7	14.5	B	NR	79.4	14.9
L	VM_f	67.0	9.4	R	VM_f	68.7	9.8
C	NR	67.7	12.8	C	NR	68.4	12.9
L	VM_f	73.0	11.8	R	VM_f	71.9	12.2
D	NR	71.8	13.7	D	NR	73.3	14.5
L	VM_f	66.7	8.4	R	VM_f	68.6	9.6
E	NR	67.9	12.6	E	NR	68.3	12.7
L	VM_f	64.0	8.9	R	VM_f	65.1	9.0
F	NR	62.3	10.6	F	NR	62.0	9.7
L	VM_f	69.9	10.6	R	VM_f	71.1	11.6
G	NR	68.5	11.4	G	NR	68.8	11.7
L	VM_f	63.4	8.2	R	VM_f	64.2	6.4
H	NR	61.4	11.1	H	NR	61.9	10.7
L	VM_f	70.7	9.8	R	VM_f	71.7	10.4
M	NR	70.5	12.5	M	NR	71.5	12.7

[a] Detector location as identified in Figure 1. LM and RM represent left and right hemispheric averages over the eight detector locations.

[b] The F_1 value for each task represents a group average over two rCBF measures for each of 12 subjects.

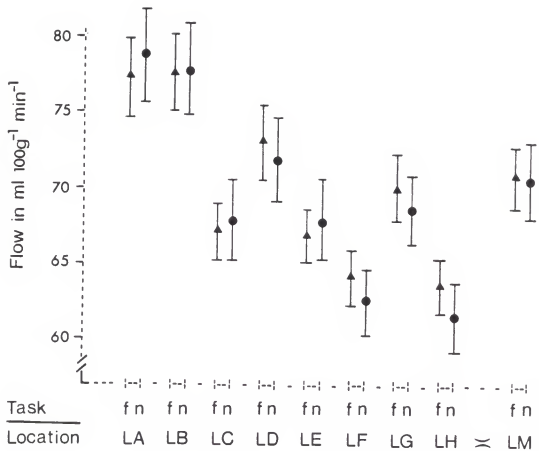

Figure 3. Results of Task Effects study for left hemisphere regions. Detector location is identified in Figure 1; LM represents the hemispheric mean. The high-rate visuomotor task (f) is indicated by triangles, the normal rest measure (n) by circles. Flow value for each task represents the $\overline{f_1}$ (ml 100 g^{-1} min^{-1}) group average over two rCBF measures for 12 subjects. Standard error of the mean is indicated for each point.

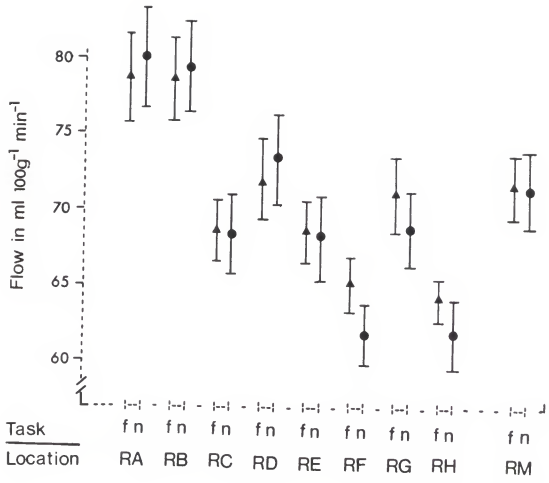

Figure 4. Results of Task Effects study for right hemisphere regions. Detector location is identified in Figure 1; RM represents the hemispheric mean. The high-rate visuomotor task (f) is indicated by triangles, the normal rest measure (n) by circles. Flow value for each task represents the f_1 (ml 100 g^{-1} min^{-1}) group average over two rCBF measures for 12 subjects. Standard error of the mean is indicated for each point.

Assessment of within-subject variance for each task was achieved by partitioning the total variance (now pooled into a Subject factor) into between-subject and within-subject (i.e., error) variance components, using the SAS (1982) VARCOMP Procedure. Table 2 contains the mean within-subject variance components for each type of task and each detector location. Comparison of the error components for each task (NR vs. VM_f) by F-ratio computation revealed significant reduction ($p(F_{12,12}) .05$) of run-to-run variability at 12 of the 16 regions during performance of the visuomotor task. Most pronounced reduction was obtained at detector locations LE and RH.

Study 2: Density Effects

The second study compares regional and hemispheric rCBF measures obtained during performance of the visuomotor task at high and low rates (VM_f and VM_s) in a second group of 12 right-handed males.

Table 3 contains the means and standard deviations of f_1 values for the VM_f and VM_s tasks at each detector location (LOC) and for the left and right hemisphere means (LM and RM). The f_1 value for each task rate represents a group average over two rCBF measures for each subject. Figures 5 and 6 present the means and standard errors of the means graphically for each hemisphere. The means of the physiologic measures, $PeCO_2$ and MABP, did not differ significantly between the VM_f and VM_s measurement conditions.

Covariate analysis for each region revealed no significant or systematic effects of age, $PeCO_2$, or MABP which were not adequately subsumed under the SUBJECT factor. Reduced-model ANOVAs for each region to test for mean flow differences due to Rate of task presentation and response (i.e., density effects) revealed significant Subject x Rate interaction at detector locations LB, RC, RG, and for left and right hemisphere means (LM and RM), along with

TABLE 2. Comparison of Mean Run-to-run (Error) Variance Components for VM_f and NR Conditions in the Task Effects Study

LEFT HEMISPHERE				RIGHT HEMISPHERE			
LOC[a]	TASK	ERROR VARIANCE	F-RATIO[b]	LOC[a]	TASK	ERROR VARIANCE	F-RATIO[b]
L	VM_f	18.0		R	VM_f	21.4	
A	NR	42.4	2.36	A	NR	39.1	1.82
L	VM_f	15.2		R	VM_f	26.3	
B	NR	43.8	2.84[c]	B	NR	55.1	2.10
L	VM_f	18.2		R	VM_f	22.5	
C	NR	57.8	3.17[c]	C	NR	56.0	2.48
L	VM_f	32.9		R	VM_f	16.6	
D	NR	25.3	1.30	D	NR	73.7	4.44[c]
L	VM_f	11.3		R	VM_f	15.8	
E	NR	81.5	7.21[d]	E	NR	74.2	4.70[c]
L	VM_f	20.2		R	VM_f	24.8	
F	NR	48.5	2.40	F	NR	49.9	2.01
L	VM_f	11.6		R	VM_f	20.3	
G	NR	35.9	3.09[c]	G	NR	64.2	3.16[c]
L	VM_f	16.6		R	VM_f	8.4	
H	NR	47.1	2.84[c]	H	NR	56.4	6.71[d]
L	VM_f	8.6		R	VM_f	8.5	
M	NR	33.2	3.86[c]	M	NR	47.8	5.62[d]

[a] Detector location as identified in Figure 1. LM and RM represent left and right hemispheric averages over the eight detector locations.

[b] Ratios are computed by dividing the larger variance by the smaller one, regardless of direction of difference.

[c] $p(>F_{12, 12})<.05$

[d] $p<.005$

TABLE 3. F_1 (ml 100 g^{-1} min^{-1}) Means and Standard Deviations for Rate Effects Group at Detector Locations Identified in Figure 1.

LEFT HEMISPHERE				RIGHT HEMISPHERE			
LOC[a]	TASK	MEAN[b]	S.D.	LOC[a]	TASK	MEAN[b]	S.D.
L	VM_f	77.3	7.4	R	VM_f	78.4	8.4
A	VM_s	78.9	11.2	A	VM_s	78.1	10.2
L	VM_f	76.5	6.7	R	VM_f	77.3	6.6
B	VM_s	78.3	10.5	B	VM_s	77.9	7.3
L	VM_f	66.7	5.9	R	VM_f	68.2	5.5
C	VM_s	67.3	8.8	C	VM_s	69.8	8.0
L	VM_f	72.4	4.5	R	VM_f	72.3	6.0
D	VM_s	74.3	6.7	D	VM_s	73.5	5.5
L	VM_f	67.1	4.6	R	VM_f	68.9	4.9
E	VM_s	68.2	6.8	E	VM_s	69.2	6.7
L	VM_f	62.7	5.8	R	VM_f	64.1	5.9
F	VM_s	63.5	7.4	F	VM_s	64.5	7.1
L	VM_f	70.3	4.8	R	VM_f	70.2	4.5
G	VM_s	71.6	6.3	G	VM_s	70.7	6.6
L	VM_f	63.0	5.2	R	VM_f	62.6	5.0
H	VM_s	63.5	7.1	H	VM_s	62.3	5.9
L	VM_f	70.5	4.7	R	VM_f	71.1	4.6
M	VM_s	71.7	7.1	M	VM_s	71.7	6.4

[a] Detector location as identified in Figure 1. LM and RM represent left and right hemispheric averages over the eight detector locations.

[b] The F_1 value for each task represents a group average over two rCBF measures for each of 12 subjects.

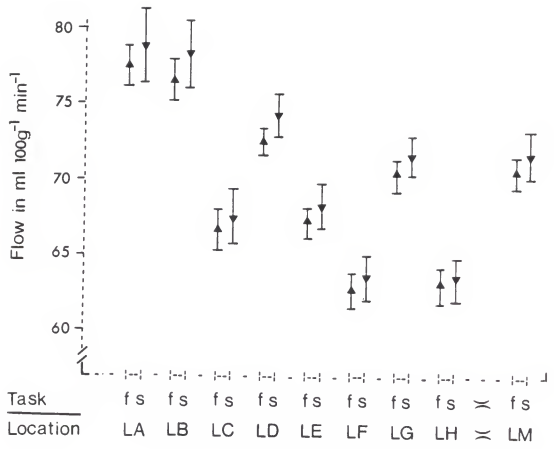

Figure 5. Results of Density Effects study for left hemisphere regions. Detector location is identified in Figure 1; LM represents the hemispheric mean. The high-rate visuomotor task (f) is indicated by triangles pointing up, the low-rate task(s) by triangles pointing down. Flow value for each task represents the $\underline{f}_1$ (ml 100 g^{-1} min^{-1}) group average over two rCBF measures for 12 subjects. Standard error of the mean is indicated for each point.

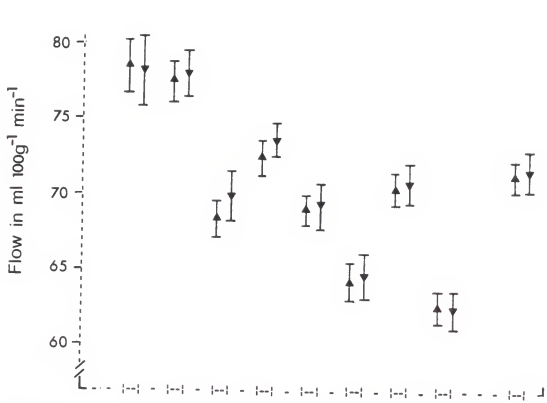

Figure 6. Results of Density Effects study for right hemisphere regions. Detector location is identified in Figure 1; RM represents the hemispheric mean. The high-rate visuomotor task (f) is indicated by triangles pointing up, the low-rate task(s) by triangles pointing down. Flow value for each task represents the $\underline{f}_1$ (ml 100 g^{-1} min^{-1}) group average over two rCBF measures for 12 subjects. Standard error of the mean is indicated for each point.

marginal effects at LD and RD. Inspection of the nonsignificant F-ratios for Rate effects revealed a suspicious number of fractional values, suggesting that the assumptions underlying the ANOVA model had not been met. Since tests for homogeneity of variance and inspection for normality of error distribution were essentially non-productive the assumption of independence of observations was examined by correlation analysis.

At those detector locations marked by significant interaction effects, the means of f_1 (within-subject) observations under the VM_f condition were not significantly related to the means of f_1 observations associated with the VM_s task. However, differences between the mean f_1 values for VM_f and the mean f_1 values for VM_s were highly and negatively correlated ($r > -.80$, $p < .001$) with the mean f_1 values for the VM_s task. This relationship is illustrated in Figure 7 for the right posterior parietal area, RG. Since the correlations between the VM_f-VM_s difference scores and the mean f_1 values for the VM_f task did not reach significant levels, the dependence is such that mean level of flow on the slow-rate visuomotor task becomes a useful predictor of amount of change expected with the high-rate task (VM_f), but not vice versa. These results suggest a functional dependence between the rCBF responses to the two measurement conditions which differed only in rate (or density) of task performance.

Partitioning of the total variance for each task into between- and within-subject components to obtain estimates of relative run-to-run variability revealed significant F-ratios ($p(> F_{12,12}) < .05$) for comparison of VM_f to VM_s at detector locations LH and RC, where variability was smaller for VM_f, the high-density task. The mean within-subject variance components for each task are displayed in Table 4 for each detector location.

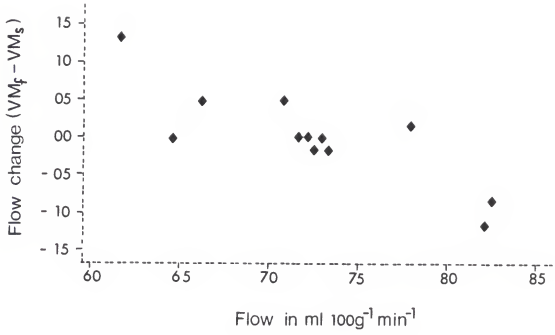

Figure 7. Example of change in flow as a function of initial level on low-rate visuomotor task. Flow change is indicated in ml 100 g^{-1} min^{-1} as the mean f_1 difference for each subject between measures during the high-rate and low-rate visuomotor tasks (VMf - VMs). Initial flow level for the slower, VMs, task is indicated on the horizontal axis. Change in flow is positive at low initial VMs levels, and negative at extremely high initial levels.

TABLE 4. Comparison of Mean Run-to-run (Error) Variance Components for VM_f and VM_s Conditions in the Density Effects Study.

LEFT HEMISPHERE				RIGHT HEMISPHERE			
LOC[a]	TASK	ERROR VARIANCE	F-RATIO[b]	LOC[a]	TASK	ERROR VARIANCE	F-RATIO[b]
L	VM_f	24.5		R	VM_f	31.2	
A	VM_s	44.1	1.80	A	VM_s	40.2	1.29
L	VM_f	24.3		R	VM_f	29.1	
B	VM_s	13.7	1.77	B	VM_s	13.7	2.12
L	VM_f	10.1		R	VM_f	8.1	
C	VM_s	22.2	2.19	C	VM_s	27.1	3.35[c]
L	VM_f	11.6		R	VM_f	20.1	
D	VM_s	21.3	1.84	D	VM_s	12.8	1.57
L	VM_f	14.7		R	VM_f	18.1	
E	VM_s	13.9	1.06	E	VM_s	20.5	1.13
L	VM_f	18.2		R	VM_f	31.0	
F	VM_s	29.2	1.60	F	VM_s	48.8	1.57
L	VM_f	14.2		R	VM_f	13.3	
G	VM_s	19.9	1.40	G	VM_s	8.5	1.56
L	VM_f	9.8		R	VM_f	8.1	
H	VM_s	27.4	2.79[c]	H	VM_s	18.7	2.30
L	VM_f	8.1		R	VM_f	7.4	
M	VM_s	9.8	1.21	M	VM_s	8.2	1.11

[a] Detector location as identified in Figure 1. LM and RM represent left and right hemispheric averages over the eight detector locations.

[b] Ratios are computed by dividing the larger variance by the smaller one, regardless of direction of difference.

[c] $p(>F_{12, 12})<.05$

Summary of Results

No treatment differences in mean level of flow due to task or task rate effects are evident in either study, except for region RF in the Task Effects (NR vs. VM_f) group. However, a marked reduction in run-to-run variability is achieved by the VM_f task in comparison to the NR condition. Significant individual differences are evident in the relative effects of the high and low rate visuomotor tasks on level of flow at several detector locations. At these regions, the mean level of flow ($\underline{f}_1$) associated with the low-rate task is inversely correlated with the mean difference in flow between the two tasks.

DISCUSSION

The results of the first study presented here have validated two of our working hypotheses: (1) that baseline data can be stabilized by having a subject perform a simple, minimal attention task in place of an eyes-closed, "non-task," "resting" baseline; and (2) that such tasks can be appropriately selected so as to create minimal regional changes of flow, in keeping with the requirements of a "good" baseline task (Stump et al., 1978). The second study has elaborated on the results of the first by examining the effects of presenting the same visuomotor controlled-rest task at two different speeds. These results demonstrate, if nothing else, the salience of individual differences in physiologic studies of brain function. They also lead us to continue to question some of the other working hypotheses upon which we build our studies.

Study 1: Task Effects

The most important results from the first study relate to the stabilization of baseline data by use of a minimal-attention visuomotor task. It is evident from the results presented in Table 2 that the VM_f task significantly reduces run-to-run variability of regional cerebral blood flow in comparison to the normal rest condition when both are given to the same subjects. Eight regions and both hemispheric means show significant reduction in variability for the visuomotor task as compared to the normal rest. The areas showing the highest variance component ratios (RH and LE) are associated with sensory-related

aspects of the stimulus presentation and task performance: Detectors "E" reflect, no doubt, metabolic activity related to sounds associated with presentation of the visual stimulus, while the right temporo-occipital detector (RH) most likely reflects the neuronal activity required for processing the visuospatial task. It is possible that, for group data, those cortical areas which are most "engaged" by the simple task may reflect this neuronal processing by a more restricted range of activity. as opposed to an overall increase in level of flow. This effect would certainly be consistent with the rationale for implementation of a sensorimotor control task in the first place. The failure to find improved reproducibility for the left perisylvian region (LD)—which should also be engaged by the right-hand thumb-press response—however, raises some question about this hypothesis. It is indeed puzzling that this area (LD) is less variable for the normal rest condition than for the visuomotor task condition. Inspection of Table 2 reveals that, for some reason, the NR error variance is particularly small at this region. Whether this is a random artifact of sampling, or a task-related phenomenon reflecting, for instance, task carryover effects, is a question which can be addressed only with further experimentation.

Since the variability across tasks and regions is on the whole greater for the Task Study group than for the Density Study group (see Tables 1 and 3), one might suspect that the apparent stabilization of run-to-run variability by the VM_f task which is notable in the Task Effects study might be simply an artifact of greater total variance for that group. However, between-group comparison of the VM_f error variance for the two groups suggests that the task itself provides run-to-run stability for repeated measures, regardless of other variability inherent in the groups. For illustration, the VM_f error variance components from the two studies are compared in Table 5, and F-ratios are computed as an index of distribution similarity. Only two regions (LD and RC)

TABLE 5. Comparison Between Two Studies: Run-to-run (Error) Variance for the VM_f Task

	LOC[a]	Density Effects Group	Task Effects Group	Between-group F-Ratios[b] (df = 12, 12)
LEFT HEMISPHERE	LA	24.5	18.0	1.36
	LB	24.3	15.4	1.58
	LC	10.1	18.2	1.80
	LD	11.6	32.9	2.84[c]
	LE	14.7	11.3	1.30
	LF	18.2	20.2	1.11
	LG	14.2	11.6	1.23
	LH	9.8	16.6	1.69
	LM	8.1	8.7	1.07
RIGHT HEMISPHERE	RA	31.2	21.4	1.48
	RB	29.1	26.2	1.11
	RC	8.1	22.5	2.78[c]
	RD	20.1	16.6	1.21
	RE	18.1	15.8	1.14
	RF	31.0	24.8	1.25
	RG	13.3	20.3	1.53
	RH	8.1	8.4	1.04
	RM	7.4	8.5	1.15

[a] Detector location for left and right hemisphere regions A-H as indicated in Fig. 1, and for the hemispheric means (LM and RM).

[b] Ratios are computed by dividing the larger variance by the smaller one, and therefore are non-directional.

[c] $p(> F) < .05$

show significant distributional differences ($p(>F)<.05$). The general equivalence of the repeated measures variance components between the two studies adds weight to the conclusion that a visuomotor control task of this kind can achieve a more reliable baseline for repeated measures studies than the eyes-closed, non-directed, normal rest condition.

The predominantly negative regional CBF findings re: task effects on mean level of flow for the first study are not totally consistent with previous findings, even from our own laboratory. The study by Leli et al. (1985) which compared a visuomotor number-recognition task to normal rest conditions did find rCBF activation effects at bilateral posterior channels G and H, as well as right hemisphere channel C, using the full curve method of analysis. That study differed from the present one in several ways, however: (1) the temporal ordering of the visuomotor task in relation to control conditions was not completely counterbalanced, (2) the visual stimuli were numeric as opposed to a spatial array of lines, (3) the stimuli were presented at an automated 7-sec. interstimulus interval versus pseudorandom 5 to 9 sec. intervals used in the current study. An earlier study (Leli et al., 1982) which used an even simpler control condition (blank slides presented automatically every 7 sec. and requiring a delayed alternation button-press response) reported control activation effects (vs. rest) at all locations except LB, LH and RD, using the partial curve method of analysis. Again, the temporal ordering of the tasks was such that the activation and control tasks were counterbalanced at positions two and three, while normal rest conditions were placed first and last.[1] Results

[1]This experimental paradigm had been implemented in order to allow adjustment for potential habituation effects over the course of the CBF session. The use of first- and fourth-position rests along with activation tasks counterbalanced at positions two and three is not criticized. It serves as an

from a recent study (judgment of line orientation) issuing from our laboratory (Hannay et al., unpublished manuscript) are more congruent with the current findings. The control task consisted of a repetitive spatial array of lines presented at a 5 to 9 sec. interstimulus rate, as in the current study, and requiring a two-choice button-press, delayed alternation response. The activation task, control task, and normal rest condition were completely counterbalanced. As in the current study, no significant changes in level of flow were found between the (visuomotor) control task and the resting baseline at any region. Of course, in all of these studies the sample size has been quite small, making generalization hazardous at best. Furthermore, the unpredictable variance of resting flow measures makes its use as a baseline condition particularly problematic under any circumstances, and makes negative results (i.e., failure to reject the null hypothesis) more likely. However, it is heartening to find a similar result using a different control task but similar experimental paradigms, even if from our own laboratory.

The possibility of differential findings between this and earlier studies due to differences in counterbalancing procedures is difficult to evaluate, since other task parameters differed as well, and the small sample size in all studies reduces predictive reliability. However, several recent studies from our laboratory have led us to suspect a non-linear trend in normal-rest measurements which is not so obvious in controlled-rest trials, but which may bias task-to-rest comparisons made solely to first and last positions.

In order to examine the possibility of mean differences in flow due to temporal position in the current task effects study, the f_1 data for each region

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adequate paradigm for assessing cognitive-task activation effects relative to the control task, and was not designed to rigorously assess the control tasks per se.

were further evaluated using a two-factor (Treatment x Run) repeated-measures ANOVA. The F-tests for overall effect of measurement were significant ($p(> F) < .05$) at left-hemisphere regions C and E, and at right-hemisphere regions C, D, E, F, and G. Post-hoc comparisons revealed the second measurement to be the highest in all regions when NR and VM_f conditions are pooled. These findings were confirmed by non-parametric analysis.

The data, then, would tend to support a second-measurement enhancement of flow across both types of measurements, a finding consistent with the recent four-normal-rest study from this laboratory (Falgout et al., 1983). The source of this effect is not clear. Prohovnik et al. (1980), using essentially the same inhalation techniques, has reported a different pattern of sequential-flow effects during same-session normal rest studies, with first and last measures tending to show the higher flow levels. Larsen et al. (1977), using the ^{133}Xe intracarotid injection procedure, reported first-run enhancement of flow which was attributed to psychophysiologic activation. Thus the sequential flow patterns may be unique both to a particular methodology as well as to a particular laboratory. We are currently examining our own calibration data as well as available physiologic and psychologic indices in an effort to increase our information regarding these "run" effects.

In continuing the comparison of Study 1 results to findings of previous studies from our laboratory, it should be noted that in addition to the differences in counterbalancing between studies, a second salient factor may lie in the nature of the two-task repeated measures (test-retest) paradigm itself: In this study, the evaluation of mean treatment effects is based on the average of two measurements under the same condition. A test given twice is not actually expected to impact upon the test-taker in the same way both times. A

plethora of explanations come to mind, among these being expectation or mental set of the subject, learning and habituation effects, changes in endogenous physiologic state, first-test apprehension or second-test boredom, contrast effects contingent on task order, and related to this, physiologic carryover or recovery effects from previous activities. Thus, aside from the fact that comparing a mean of two measurements under one condition to the mean of two measurements under a second condition certainly offers the most conservative measure of differences between treatment a priori, there is the further possibility that both level of engagement and variability in task performance are influenced by the subject's initial (informed) expectations regarding same-task repetition. The "boredom factor," for example, may be enhanced by the expectation of performing a pair of monotonous and low-demand tasks not once but twice during a two-hour session, and may result in individual (creative) responses which further mask any "task" effects per se.

Whatever the mechanism, it seems likely that counterbalancing contributes to the obfuscation of otherwise identifiable, though evidently not robust, task effects, and conversely, that sensorimotor "task" effects may become most apparent when other parameters are set. It may be argued of course that "task" effects obtained under such standardized conditions are not "task" effects at all, but perhaps "order" effects or "contrast" effects, or "run-two" effects, for example. And in a certain scientific sense, that argument would be accepted. However, in an equally pure and irreproachable scientific sense, the opposite argument may be true: in order to demonstrate certain lawful phenomena which might otherwise escape our notice, certain other influential factors must be controlled. Thus, the constant effects of "gravity" on a falling mass are more apparent under a variety of atmospheric conditions when a stone is the object observed falling, as opposed to a feather. If the

constancy of gravitational effect is to be demonstrated with a feather, certain relevant environmental parameters must be rigorously controlled.[2]

For the sake of completeness, the one positive finding from the first study regarding visuomotor task effects on mean level of flow as compared to normal rest must be addressed: the finding of VM_f versus NR activation over the right inferior temporal region. Our other studies have typically not reported results from this detector location (F), since its relative placement in the fixed-detector montage makes it the most vulnerable to positioning artifact, and because it has sometimes shown high variability relative to other detectors. However, the means and variances obtained from the "F" detectors in this study are compatible with those from the contiguous temporo-occipital detectors (H) in the eyes-closed (resting) condition (see Table 1 and Fig. 1), so the data cannot be discarded lightly as artifactual. The location of the detector over the middle and inferior aspects of the temporal lobe, moreover, puts it in a position to monitor cortical areas which have been shown in lesion studies to affect complex spatial learning tasks in the monkey (Cowey & Gross, 1970). There is neuroanatomical evidence that suggests these regions may be involved in automatic scanning and identification of spatial stimuli which will be acted upon by other components of the spatial memory system (Pandya & Yeterian, 1984). This positive finding, then, though interpreted cautiously dueto the high probability of spurious effects related to multiple comparison procedures and small sample size, must nevertheless be recognized as plausible and held up for possible verification from other studies.

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[2]I am indebted to Hays (1962, p. 42) for reminding me of Galileo's insightful disregard of appearance in his search for constancy. Lesser scientists among us depend more heavily on demonstration than on logic. To such minds, the "proof" of the relationship depends, in the end, on strict "experimental" control, not on counterbalancing or other methods for distributing the variance.

Study 2: Density Effects

As for the effects of task rate on level of flow, the results from the second study are clear: (a) individual differences in response to rate of task presentation are of considerable importance, and (b) there is apparently an inverse relationship between regional flow values at the lower task rate and differential rCBF response to the higher rate of performance. In other words, those subjects with the highest flow rates for the VM_s task tended to show the smallest mean increases—or even to show decreases in flow levels—when presented with the high-rate VM_f task; those subjects with the lowest flow rates for the VM_s task showed the largest mean increases to the high-rate task.

The individual variation in rCBF responses to the two rates of task presentation are by no means surprising. Some of the spontaneous comments made by the subjects as they completed the four task-related rCBF measures illustrate the very individualized reactions elicited by the two rates of task presentation: Two subjects were irritated by the high-rate task, as it interfered with their ongoing ideational or imaginal processes; another much preferred that task as it held his attention better than the slower one; a fourth used the changing visual array as an aid in self-initiated meditation; still another created his own test paradigm by trying to guess what stimulus pattern would turn up next. It is attractive to believe that these creative and idiosyncratic responses to what could otherwise be considered a pair of "cold" cognitive tasks would be reflected in physiologic measures of brain work, if we but knew how to ferret out the information. Alternatively, it is certainly plausible and potentially more useful, to hypothesize that the physiologic response may inform us regarding the prediction of individual differences.

The Law of Initial Value, first described by Wilder (1931, cited by Wilder, 1957) and elaborated by Lacey (1956) appears to accurately describe the pattern of these rCBF responses to differing task rates. Loosely defined, this law states that higher initial levels of activation in a given physiologic system are associated with smaller changes in response to additional stimulation. A corollary is that at extreme levels of activation, the response to stimulation is more likely to be a "paradoxical" one, reversing its typical direction. Recently, Rogers et al. (1985) have demonstrated the application of the Law of Initial Value to the vasomotor reactivity of the cerebrovascular system as measured by rCBF.

It is notable that the initial-value relationship is not apparent in the first of these studies, comparing the NR to the VM_f task. In that comparison, knowledge of the average level of flow during the NR condition does not facilitate prediction of the change in flow due to visuomotor stimulation. It is possible that the greater intrinsic variability of resting measures obscures the subtle effects of changes due to the minimally-demanding visuomotor task. If this is true, then stabilization of the regional blood flow measures by use of the controlled rest task allows these individual differences in task response to become manifest and measurable.

The results of the variance component analysis of the Density study suggest that there is little additional gain in stability of rCBF measures when the high-rate visuomotor task is compared to the low-rate task (see Table 4); only two detector locations (LH and RC) show significantly lower variability under the more demanding conditions. It is speculative but reasonable to interpret these focal results (along with other areas showing near-significant variance ratios) as reflecting increased stimulus-bound attentional and visuospatial activity.

The finding that individual differences are paramount in prediction of rCBF responses to differing rates of task performance—even for these very simple visuomotor tasks—demands that we re-assess both our experimental design and our interpretation of task-related activation effects in studies evaluating higher cognitive processing. Although some tasks may be easily designed so that the sensorimotor control condition very nearly duplicates the sensory and motor requirements of the test condition (except, naturally, for level of difficulty), other tasks (such as Miller Analogies) are not nearly so amenable to matched-rate sensorimotor control stimulation. In these cases, it may be necessary to impose a form of statistical control, such as partial correlation, in order to sort out the higher cognitive from the more purely sensorimotor aspects of task performance.

General Issues

Several points remain to be made about the methods of data analysis used in this study. The evaluation of task-related changes in level of flow and run-to-run reproducibility of flow has been done on a region-by-region basis; that is, the question addressed is whether focal flow in a given region "X" changes significantly as a result of type of task administered during the rCBF measurement. No consideration is given to definition of that region's relative flow level with respect to another. Thus, an f_1 increase in region "X" associated with performance of the visuomotor task may reflect any of several phenomena of interest. This "isolationist" approach does not allow discrimination between (a) a general hemispheric or global change in level of flow reflected at all or most detector locations, and (b) a local and specific change in flow which may or may not be correlated—inversely or directly—with changes in other regions of interest. Nor does this approach allow a definition

of any particular pattern or profile of flow across the regions of interest which might be associated with a particular type of task, or with person x task interactions. Although such patterns may be more readily ascertained by the implementation of three-dimensional visual displays such as the tomographic maps available with P.E.T. technology, the assessment of relevant task-related changes must still rely on application of appropriate statistical (decision-making) procedures as well as comparison to relevant baseline or normative data.

The difficulties inherent in application of common statistical procedures to a set of data which may be both restricted in quantity and highly intercorrelated are not unique to the ^{133}Xe methodology. Several recent publications in the three-dimensional physiologic imaging literature have begun to address these issues. Multivariate procedures dependent on regression approaches (including ANOVA) suffer from the common problem, in these radioisotopic studies, of inadequate sample sizes. As the quantity of data per individual is increased, however, the adaptation and application of Q-type factor-analytic methods may provide a more promising approach to data definition and analysis (Clark et al., 1985).

In focusing on the task-related aspects of run-to-run variability in these studies, I have ignored the more general issue relating to other sources of extraneous variability in rCBF measurement by the ^{133}Xe inhalation technique. This issue has not been ignored in the rCBF literature, however (e.g., Ingvar & Lassen, 1982; McHenry et al., 1978; Prohovnik et al., 1980), nor is it overlooked in the rapidly expanding literature of the various three-dimensional imaging technologies. The sources of variance are broad, ranging from fluctuating detector sensitivity to mathematical modeling algorithms to respiratory efficiency to circadien and ultradien fluctuations in level of arousal. The most

powerful and uncontrolled determinant of level of flow, however, appears to relate to the intrinsically determined physiologic (cognitive/emotive) state of the individual (Blauenstein et al., 1977; Mchedlishvili, 1980), and this influence appears to be most evident and unpredictable in normal subjects in the various states of arousal associated with sleep and dreaming. Thus the decision to consider these sources of variance as non-random is the first step toward gaining control over them. The use of alternative baseline tasks—instead of or in addition to the non-directed "normal rest"—is seen as instrumental in bringing this important source of variance under some degree of experimental control.

Summary

The results of these two within-group, within-subject studies have demonstrated the effectiveness of a simple visuomotor task in reducing run-to-run variability of regional and hemispheric blood flow measures as compared to the standard eyes-closed resting baseline condition, and have highlighted the importance of individual differences in response to differing rates of task presentation. The use of a within-subject experimental design enables the assignment of a degree of credibility to these findings which would not be as definitive in a small-sample, between-group reliability study. These findings certainly have implications for other physiologic methodologies used in the investigation of metabolic parameters related to human brain function, as well as for the ^{133}Xe inhalation technique of measuring cerebral blood flow in particular. The hypothesized stabilizing function of a controlled rest condition in sequential studies—and of its alias, the sensorimotor control task in studies of complex cognitive processes—is validated by these studies.

REFERENCES

Blauenstein, U.W., Halsey, J.H., Wilson, E.M., Wills, E.L., & Risberg, J. 1977. Xenon-133 inhalation method, analysis of reproducibility: some of its physiological implications. Stroke 8:92-102.

Clark, C., Carson, R., Kessler, R., Margolin, R., Buchsbaum, M., DeLisi, L., King, C., & Cohen, R. 1985. Alternative statistical models for the examination of clinical positron emission tomography/fluorodeoxyglucose data. Journal of Cerebral Blood Fow and Metabolism, 5:142-150.

Cowey, A., & Gross, C.G. 1970. Effects of foveal prestriate and inferotemporal lesions on visual discrimination by Rhesus monkeys. Exp. Brain Res. 11:128-144.

Falgout, J.C., Leli, D.A., & Halsey, J.H., Jr. 1983. Observations on variability in the "resting" brain: A descriptive rCBF study. Poster session presented at the meeting of the International Neuropsychological Society, Mexico City.

Falgout, J.C., Leli, D.A., Hannay, H.J., & Halsey, J.H., Jr. 1984. Issues in physiologic assessment of human cerebral activity: Alternatives to the normal resting baseline. Paper presented at the meeting of the Southeastern Psychological Association, New Orleans.

Fox, P.T., & Raichle, M.E. 1984. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. Journal of Neurophysiology 51(5):1109-1120.

Gur, R.C., Gur, R.E., Rosen, A.D., Warach, S., Alavi, A., Greenberg, J., & Reivich, M. 1983. A cognitive-motor network demonstrated by positron emission tomography. Neuropsychologia 21(6):601-606.

Gur, R.C. & Reivich, M. 1980. Cognitive task effects on hemispheric blood flow in humans. Brain and Language 9:78-92.

Halsey, J.H., Jr., Blauenstein, U.W., Wilson, E.M., & Wills, E.L. 1979. Regional cerebral blood flow comparison of right and left hand movement. Neurology 29: 21-28.

Halsey, J.H., Blauenstein, U.W., Wilson, E.M., & Wills, E.L. 1980. Brain activation in the presence of brain damage. Brain and Language 9: 47-60.

Hannay, H.J., Leli, D.A., Falgout, J.C., Katholi, C.R., & Halsey, J.H., Jr. 1983. rCBF for middle-aged males and females during right-left discrimination. Cortex 19:465-474.

Hays, W.L. 1962. Statistics. New York: Holt, Rinehart & Winston, 719 pp.

Hazelrig, J.B., Katholi, C.R., Blauenstein, U.W., Halsey, J.H., Wilson, E.M., & Wills, E.L. 1981. Total curve analysis of regional cerebral blood flow with ^{133}Xe inhalation: Description of method and values obtained with normal volunteers. IEEE Transactions on Biomedical Engineering 28: 609-616.

Ingvar, D. H., & Lassen, N. A. 1982. Atraumatic two-dimensional rCBF measurments using stationary detectors and inhalation or intravenous administration of 133-xenon (Editorial). Journal of Cerebral Blood Flow and Metabolism, 2:271-274.

Ingvar, D.H., & Risberg, J. 1965. Influence of mental activity upon regional cerebral blood flow in man. Acta Neurologica Scandinavica 41(Suppl 14), 43-96.

Ingvar, D.H., & Risberg, J. 1967. Increase of regional cerebral blood flow during mental effort in normals and in patients with focal brain disorders. Experimental Brain Research 3: 195-211.

Lacey, John I. 1956. The evaluation of autonomic responses: Toward a general solution. Ann NY Acad Sci 67: 125-163.

Larsen, N.A., Roland, P.E., Larsen, B., Melamed, E., & Soh, K. 1977. Mapping of human cerebral functions: A study of the regional cerebral blood flow pattern during rest, its reproducibility and the activations seen during basic sensory and motor functions. Acta Neurologica Scandinavica 56(Suppl. 6a): 262-263.

Leli, D.A., Hannay, H.J., Falgout, J.C., Wilson, E.M., Wills, E.L., Katholi, C.R., & Halsey, J.H., Jr. 1982. Focal changes in cerebral blood flow produced by a test of right-left discrimination. Brain and Cognition 1: 206-223.

Leli, D.A., Hannay, H.J., Falgout, J.C., Katholi, C.R., & Halsey, J.H., Jr. 1983. Age effects on cerebral blood flow changes produced by a test of right-left discrimination. Neuropsychologia 21: 525-533.

Leli, D.A., Hannay, H.J., Falgout, J.C., Katholi, C.R., Wilson, E.M., Wills, E.L., & Halsey, J.H., Jr. 1984. Relevance of sensorimotor task components to the interpretation of task related blood flow changes. Neuropsychologia 22: 79-84.

Leli, D.A., Katholi, C.R., Hazelrig, J.B., Falgout, J.C., Hannay, H.J., Wilson, E.M., Wills, E.L., and Halsey, J.H., Jr. 1985. Measurement of activated rCBF by the ^{133}Xe inhalation technique: A comparison of total versus partial curve analysis. Stroke 16(2):274-282.

Mallett, B.L. and Veall, N. 1965. The measurement of regional cerebral clearance rates in man using xenon-133 inhalation and extracranial recording. Clinical Science 29:179-191.

Maximilian, V.A. 1980. Functional changes in the cortex during mental activation. Applications of regional cerebral blood flow measurements in neuropsychological research. Doctoral thesis, University of Lund, Sweden.

Mchedlishivili, G. 1980. Physiological mechanisms controlling cerebral blood flow. Stroke 11:240-248.

McHenry, L.C., Jr., Merory, J., Bass, E., Stump, D.A., Williams, R., Witcofski, R., Howard, G., & Toole, J.F. 1978. Xenon-133 inhalation method for regional cerebral blood flow measurements: Normal values and test-retest results. Stroke 9(4):396-399.

McLain, C.A., Wolfe, S.E., Falgout, J.C., Leli, D.A., & Katholi, C.R. 1984. One week test-retest reliability of regional cerebral blood flow activation of a verbal task. Paper presented at the meeting of the International Neuropsychological Society, Houston.

Meyer, J.S., Ishihara, N., Deshmukh, V.D., Naritomi, H., Sakai, F., Hsu, M.-C., & Pollack, P. 1978. Improved method for noninvasive measurement of regional cerebral blood flow by ^{133}Xenon inhalation. Part I: Description of method and normal values obtained in healthy volunteers. Stroke 9(3):195-205.

Myers, J.L. 1972. Fundamentals of experimental design (2nd Ed.). Boston: Allyn and Bacon, 465 pp.

Obrist, W.D., Thompson, H.K., Jr., King, C.D., and Wang, H.W. 1967. Determination of regional cerebral blood flow by inhalation of ^{133}xenon. Circulation Research 20:124-135.

Obrist, W.D., Thompson, H.K., Wang, H.S., & Wilkinson, W.E. 1975. Regional cerebral blood flow estimated by ^{133}xenon inhalation. Stroke 6: 245-256.

Pandya, D.N., & Yeterian, E.H. 1984. Proposed neural circuitry for spatial memory in the primate brain. Neuropsychologia, 22:109-122.

Prohovnik, I, Hakansson, K., & Risberg, J. 1980. Observations on the functional significance of regional cerebral blood flow in "resting" normal subjects. Neuropsychologia 18:203-217.

Raichle, M.E., Grubb, R.L., Gado, M.H., Eichling, J.O., & Ter-Pogossian, M.T. 1976. Correlation between regional cerebral blood flow and oxidative metabolism. Archives of Neurology 8: 523-526.

Reivich, M., Obrist, W.D., Slater, R., Greenberg, J., and Goldberg, H.I. 1975. A comparison of the ^{133}Xe intracarotid and inhalation techniques of measuring cerebral blood flow. In A.M. Harper, W.B. Jennett, J.D. Miller,

and R.O. Rowan (Eds.), Blood flow and metabolism in the brain. New York: Churchill Livingstone, pp. 8.3-8.6.

Risberg, J., Halsey, J.H., Wills, E.L., & Wilson, E.M. 1975. Hemispheric specialization in normal man studied by bilateral measurements of the regional cerebral blood flow. A study with the 133-Xe inhalation technique. Brain 98: 511-524.

Risberg, J., & Ingvar, D.H. 1972. Multibulbous technique for measuring the distribution of cerebral blood flow over short intervals in man. Circulation Research 31: 889-898.

Risberg, J., & Ingvar, D.H. 1973. Patterns of activation in the grey matter of the dominant hemisphere during memorization and reasoning. A study of regional cerebral blood flow changes during psychological testing in a group of neurologically normal subjects. Brain 96: 751-756.

Risberg, J., Maximilian, A.V., & Prohovnik, I. 1977. Changes of cortical activity patterns during habituation to a reasoning task. Neuropsychologia 15:793-798.

Rogers, R.L., Meyer J.S., Mortel, K.F., Mahurin, R.K., & Thornby, J. 1985. Age-related reductions in cerebral vasomotor reactivity and the Law of Initial Value: A 4-year prospective longitudinal study. Journal of Cerebral Blood Flow and Metabolism 5(1): 79-85.

Roland, P.E. & Skinhoj, E. 1981. Extrastriate cortical areas activated during visual discrimination in man. Brain Research 222:166-171.

SAS Institute, Inc. 1982. SAS user's guide: Statistics, 1982 edition. Cary, NC: SAS Institute, Inc., 584 pp.

Stump, D.A., Cooke, N., Yonovitz, A., Perez, F.I., & Meyer, J.S. 1978. Selective regional cerebral blood flow responses to auditory stimuli: White noise versus human voice. Presented at the Ninth International Salzburg Conference on Cerebrovascular Disease, Salzburg, Austria.

Veall, N. and Mallett, B.L. 1966. Regional cerebral blood flow determination by ^{133}xenon inhalation and external recording: The effect of arterial recirculation. Clinical Science 30:353-369.

Wilder, J. 1931. The "Law of Initial Value," a neglected biologic law and its importance for research and practice. Zeitschrift für die gesammte neurologie und psychiatrie 137:317 (cited by Wilder, 1957).

Wilder, J. 1957. The law of initial value in neurology and psychiatry: Facts and problems. J. Nervous & Mental Disease, 125:73-86.

Wilson, E.M., Wills, E.L., Risberg, J., Halsey, J.H., Gerard, J.D., & May, C.P. 1977. Measurement of regional cerebral blood flow by the ^{133}Xenon inhalation method with an on-line computer. Computers in Biology and Medicine 7:143-157.

Winer, B.J. 1971. Statistical principles in experimental design (2nd Ed.). New York: McGraw-Hill, 907 pp.

Wood, F. 1980. Theoretical, methodological, and statistical implications of the inhalation rCBF technique for the study of brain-behavior relationships. Brain and Language 9:1-8.

Wood, F., Taylor, B., Penny, R., & Stump, D. 1980. Regional cerebral blood flow response to recognition memory versus semantic classification tasks. Brain and Language 9:113-122.

BIOGRAPHICAL SKETCH

Janet Copeland Falgout was born July 21, 1942, and raised in West Florida. She earned both her baccalaureate and master's degrees from the University of Florida in 1967 and 1975, respectively, specializing in physiologic and experimental psychology. Her doctoral studies in the University of Florida's Department of Clinical Psychology and her clinical internship at the University of Alabama at Birmingham Medical School have culminated in a major research and clinical focus on physiologic and neuropsychologic aspects of human behavior. Since her internship, she has completed a predoctoral fellowship in the UAB Department of Neurology/Division of Neuropsychology and is currently employed there as a Research Associate.

Working for a number of years at the University of Florida's Visual Science Laboratory under Drs. N. W. Perry and D. G. Childers, Ms. Falgout gained some expertise in electrophysiologic measures of perception and development. Her affiliation with the UAB Stroke Research Center has allowed her to acquire some experience with the cerebral blood flow methodology as a tool in neurobehavioral research. At UAB, she has collaborated with Dano Leli, Ph.D., James Halsey, Jr., M.D., and Julia Hannay, Ph.D. (Auburn University), in refining experimental paradigms for the application of cerebral blood flow methodology to the study of human cognitive processes.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Eileen B. Fennell
Associate Professor of Clinical Psychology

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Jacquelin R. Goldman
Professor of Clinical Psychology

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Russell M. Bauer
Associate Professor of Clinical Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Hugh C. Davis
Professor of Clinical Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Edward Valenstein
Professor of Neurology

This dissertation was submitted to the Graduate Faculty of the College of Health Related Professions and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1985

Dean, College of Health Related Professions

Dean, Graduate School